IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant -	David J. Fink, Salvatore T. DiNovo, and Thomas J. Ward	:Examiner: R. Shay
Serial No.-	07/929,449	:Group Art Unit: 3308
Filed -	August 14, 1992	:
For -	Rapid, Customized Bone Prosthesis	:Responsive to the office action mailed 10/26/93

I hereby certify that this correspondence is being deposited with the United States Postal Service as first class mail in an envelope addressed to: Commissioner of Patents and Trademarks, Washington, D.C. 20231, on 2-28-94

Frank H. Foster

2-28-94
Date of Signature

Commissioner of Patents and Trademarks
Washington, D.C. 20231

Honorable Sir:

RULE 131 AFFIDAVIT

I, Salvatore T. DiNovo, state that I am an inventor in the above-identified patent application and hereby further state as follows:

1. The invention described and claimed in the above-identified patent application was conceived by us prior to

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ATTORNEYS AT LAW
PATENTS, TRADEMARKS AND COPYRIGHTS
7632 SLATE RIDGE BLVD.
REYNOLDSBURG, OH 43068
(614) 575-2100

August 24, 1992.

2. Exhibit A is an outline of proposed research projects for the present invention and was prepared by David J. Fink, one of the inventors, on or before March 5, 1992.

3. Exhibit B is a copy of a document prepared by David Fink and sent to me on or before March 12, 1992, outlining the concept of the invention.

4. Appended hereto and marked Exhibit C is a copy of an SBIR Grant Application which was prepared by me and under my supervision and, after having been completed, was signed by me on April 14, 1992. This application additionally included copies of letters from others and budget materials which have been excised from the exhibit and are not relevant to the conception of the invention. Additionally, certain financial data has been obliterated.

5. The application of Exhibit C was submitted to the National Heart, Lung and Blood Institute during the week of April 14, 1992.

6. Exhibit D is a letter to our patent attorney enclosing other documents which included a copy of a letter of March 23, 1992 to the Commander of the U.S. Army Medical Research and Development Command and a copy of the enclosure in that letter to the Command. The letter to our attorney was mailed on March 24, 1992 and the March 23 letter and its enclosure were sent on March 23, 1992 to the Commander.

7. Exhibit E is a copy of a document prepared by Tom

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Ward, an inventor in the above application, sent by fax to me on April 2, 1992 and outlining a plan for a research project in connection with the present invention.

8. Exhibit F is an outline of a research proposal prepared by David Fink, also an inventor, on or before April 7, 1992.

9. Exhibit G is a transmittal letter and accompanying proposal for research in connection with the present invention received to me and accepted and signed by me on April 8, 1992.

10. During the time period following April 7, 1992 and ending September 18, 1992, the research proposed by Tom Ward in Exhibit G was carried out. In addition, during that same time interval the inventors met periodically to discuss the invention and the activities in the research project.

11. The research project was completed by and a report summarizing those research efforts was transmitted to me by letter of September 18, 1992, a copy of which is appended as Exhibit H.

The undersigned, Salvatore T. DiNovo, declares: that all statements made herein of his own knowledge are true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both under Section 1001

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of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent resulting therefrom.

February 25, 1994
Date of Signature

Salvatore T. DiNovo

Our File No.: GUI 108

Enclosures: Exhibits A-H

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Ser. # 07/929,449 EXHIBIT A

GUILD Rapid Manufacturing Technology Project 3-5-92 / DJF

CANDIDATE PHASE-1 PROJECTS

1. CT to CAD to RMT Demonstration

   - Convert low resolution CT file(s) to solid model CAD
   - Slice CAD file
   - Prepare RMT device(s)
   - Compare 2 or more RMT processes with standard CAD file

2. Produce "porous" ceramic devices by RMT

   - Create CAD files of standard geometry with designed micro-porosity
   - Slice CAD files
   - Prepare RMT devices
   - Characterize porosity of RMT devices & compare to design file

3. Compare Structural and Mechanical Properties of Trabecular Bone & RMT Analogs

   - Convert CT files of trabecular bone to solid model CAD files
   - Slice CAD files
   - Prepare ceramic and polymeric RMT devices
   - Characterize structures of RMT devices by CT & compare to trabecular bone
   - Characterize mechanical properties of RMT devices by standard tensile tests, etc. & compare to trabecular bone

4. Characterize Biocompatibility of Ceramic RMT Materials

   - Prepare porous & nonporous devices by ceramic RMT
   - Obtain similar samples of standard biomedical materials (hydroxy apatite; calcium carbonate)
   - Implant/extract samples of each & compare biological responses (Class VI Testing)
   - Culture osteogenic cells on each material & compare <u>in vitro</u> response
   - Seed samples of each material with Mesenchymal Stem Cells and implant in ectopic rat model
   - Determine rate of ceramic resorption in vivo (gravimetric, histological, CT)

5. Fabrication of New Engineering Devices for Gas-Gas Separations (Non-Medical)

   - Design solid model CAD file of fractal porous bed of same adsorbent used for O_2-N_2 pressure swing separations
   - Prepare RMT device from this fractal file
   - Prepare bed of same mass (volume?) of adsorbent for control
   - Compare efficiency of separation of the RMT & control devices in standard pressure swing adsorption process

Ser. # 71929, 4/4/9

EXHIBIT B

Fax Transmittal Memo 7672

To TED DiNOVO
Company Guild Associates
Location
Fax # 876-5828 Telephone #
Comments

No. of Pages 5 Today's Date 3-12-92 Time 3:25 pm
From David Fink
Company CollaTek, Inc.
Location Dept. Charge
Fax # 294-1002 Telephone # 299-1717
Original Disposition: ☐ Destroy ☐ Return ☐ Call for pickup

I'm including several of the documents we have discussed. DF

Attach Document At Line

Guild Associates Concept Paper

Use of Rapid Manufacturing Techniques for Customized Hard Tissue Reconstruction

Guild Associates has identified a strategy for a new therapeutic approach that will provide customized prosthetic devices for hard tissue reconstruction. Guild believes that rapid manufacturing technology can produce implants that reproduce original tissue size and shape, and that maximize the rate and of cell-mediated hard tissue healing. The Guild concept requires integration of several independently developing technologies to produce implants 1) designed to provide the physical characteristics of the patient's original hard tissue, and 2) constructed to optimize the rate of healing by incorporating the patient's own bone-producing cells into the implant. Steps in the process would be:

Imaging Technology

1) Define hard tissue characteristics (size, shape, porosity, etc.) before the trauma occurs ("pre-trauma file") by archival use of available imaging techniques (CT, MRI, etc.).
2) Define loss of hard tissue by imaging in the locale of the affected tissue after the injury ("post-trauma file").
3) Specify the physical properties of the customized prosthetic device by comparison of the pre-trauma and post-trauma files to produce a solid model "design file". This specification may also involve secondary manipulation of the files to assist in surgical implantation and to compensate for anticipated healing processes.

Rapid Manufacturing Technology

4) Mathematically process the design file to produce a "sliced file" that is then

used to direct a "rapid manufacturing" system to construct a precise replica of the design file in a resorbable ceramic material to produce the implant.

Autologous Cell Therapy

5) Culture autologous cells, derived from the patient's pre- or post-trauma tissue, then "seed" the cells onto the ceramic matrix under conditions appropriate to maximize cell attachment and function. The implanted cells will rapidly begin to produce new bone tissue, and to slowly degrade the ceramic matrix.
6) Implant the cell-seeded prosthesis at the trauma site, and begin appropriate rehabilitation therapy.

EXHIBIT C

OMB No. 0925-0195
Expiration Date 1/31/95

Department of Health and Human Services
Public Health Service

Small Business Innovation Research Program
PHASE I GRANT APPLICATION

Follow instructions carefully.

Leave blank – for PHS use only.		
Type	Activity	Number
Review Group		Formerly
Council Board *(Month, year)*		Date Received

1. TITLE OF APPLICATION *(Do not exceed 56 typewriter spaces)*
Free Form Manufacturing of Medical Devices

2. SBIR SOLICITATION NO. SBIR 92-2

3. PRINCIPAL INVESTIGATOR ☐ New Investigator

3a. NAME *(Last, first, middle)*
Mr. Thomas Ward

3b. SOCIAL SECURITY NO.
273-46-7873

3c. POSITION TITLE
Senior Research Engineer

3d. MAILING ADDRESS *(Street, city, state, zip code)*
Guild Associates, Inc.
4089 North Leap Road
Hilliard, Ohio 43026

3e. TELEPHONE AND FAX *(Area code, number, and extension)*
TEL: (614) 876-5252
FAX: (614) 876-5828

4. HUMAN SUBJECTS — If "Yes," exemption no. or IRB approval date — 4b. Assurance of compliance no.
4a. [X] NO [ ] YES

5. VERTEBRATE ANIMALS — If "Yes," IACUC approval date — 5b. Animal welfare assurance no.
5a. [X] NO [ ] YES

6. DATES OF PROJECT PERIOD
From: Nov. 1, 1992 *Through:* April 30, 1993

7. COSTS REQUESTED
7a. Direct Costs $ [redacted] 7b. Total Costs [redacted]

8. PERFORMANCE SITES *(Organizations and addresses)*
Guild Associates, Inc.
4089 North Leap Road
Hilliard, Ohio 43026

9. APPLICANT ORGANIZATION *(Name, address, and congressional district)*
Guild Associates, Inc.
4089 North Leap Road
Hilliard, Ohio 43026
Ohio's 15th Congressional District

10. ENTITY IDENTIFICATION NUMBER
1310998683A1

11. SMALL BUSINESS CERTIFICATION
[X] Small business
[ ] Minority and disadvantaged [ ] Woman-owned

12. NOTICE OF PROPRIETARY INFORMATION: The information identified by asterisks (*) on pages _____ of this application constitutes trade secrets or information that is commercial or financial and confidential or privileged. It is furnished to the Government in confidence with the understanding that such information shall be used or disclosed only for evaluation of this application, provided that, if a grant is awarded as a result of or in connection with the submission of this application, the Government shall have the right to use or disclose the information herein to the extent provided by law. This restriction does not limit the Government's right to use the information if it is obtained without restriction from another source.

14. NAME OF CORPORATE OFFICIAL
TELEPHONE (614) 876-5252
FAX: (614) 876-5828
TITLE: Mr. S. T. (Ted) DiNovo
ADDRESS: President
Guild Associates, Inc.
4089 North Leap Road
Hilliard, Ohio 43026

13. DISCLOSURE PERMISSION STATEMENT: If this application does not result in an award, is the Government permitted to disclose the title only of your proposed project, and the name, address, and telephone number of the corporate official of your firm, to organizations that may be interested in contacting you for further information or possible investment?
[X] YES [ ] NO

BITNET/INTERNET ADDRESS:

15. PRINCIPAL INVESTIGATOR ASSURANCE: I agree to accept responsibility for the scientific conduct of the project and to provide the required progress reports if a grant is awarded as a result of this application. Willful provision of false information is a criminal offense (U.S. Code, Title 18, Section 1001). I am aware that any false, fictitious, or fraudulent statement may, in addition to other remedies available to the Government, subject me to civil penalties under the Program Fraud Civil Remedies Act of 1986 (45 CFR 79).

SIGNATURE OF PERSON NAMED IN 3a *(In ink. "Per" signature not accepted.)* — DATE 04/14/92

16. CERTIFICATION AND ACCEPTANCE: I certify that to the best of my knowledge and belief the statements herein are true, accurate, and complete, and I accept the obligation to comply with the Public Health Service terms and conditions if a grant is awarded as the result of this application. A willfully false certification is a criminal offense (U.S. Code, Title 18, Section 1001). I am aware that any false, fictitious, or fraudulent statement may, in addition to other remedies available to the Government, subject me to civil penalties under the Program Fraud Civil Remedies Act of 1986 (45 CFR 79).

SIGNATURE OF PERSON NAMED IN 14 *(In ink. "Per" signature not accepted.)* — DATE 4/14/92

SN 07/929,899

ABSTRACT OF RESEARCH PLAN

NAME, ADDRESS, AND TELEPHONE NUMBER OF APPLICANT ORGANIZATION

Guild Associates, Inc.
4089 North Leap Road
Hilliard, Ohio 43026

YEAR FIRM FOUNDED	NO. OF EMPLOYEES *(include all affiliates)*
1981	30

TITLE OF APPLICATION
Free Form Manufacturing of Medical Devices

KEY PROFESSIONAL PERSONNEL ENGAGED ON PROJECT

NAME	POSITION TITLE	ORGANIZATION
Thomas J. Ward, M.S., P.E.	PI/Senior Research Engineer	Guild Associates, Inc.
David Fink, Ph. D.	Medical Device Consultant	Bio–Integration, Inc.
S. T. DiNovo, M.S. Ch.E., P.E	Senior Internal Manager	Guild Associates, Inc.

ABSTRACT OF RESEARCH PLAN: State the application's long-term objectives and specific aims, making reference to the health-relatedness of the project, describe concisely the methodology for achieving these goals, and discuss the potential of the research for technological innovation and commercial application. Avoid summaries of past accomplishments and the use of the first person.

The abstract is meant to serve as a succinct and accurate description of the proposed work when separated from the application. Since abstracts of funded applications may be published by the Federal Government, do not include proprietary information. DO NOT EXCEED 200 WORDS.

It has been only slightly more than two decades since the discovery by Hench and his co-workers that a direct chemical bond can form between certain "bioactive" glass–ceramic materials and bone, thereby potentially stabilizing dental or orthopaedic implants made from these materials. In the meantime, the investigation of other chemical formulations (including many ceramics and composities), physical forms (e.g., dense or porous particulates and solids, coatings, and composites), and clinical applications have progressed rapidly.

Guild Associates has identified a strategy for a new manufacturing approach that will provide customized prosthetic devices for hard tissue reconstruction. The concept requires integration of several independently developing technologies into a novel integrated system. The company's goal is to develop a new method for fabricating customized medical implant devices by serving as the focus for integrating the component technologies. It is anticipated that this amalgamation of technologies will then be offered to the general orthopedic and dental communities as a specialized service.

Provide key words (8 maximum) to identify the research or technology.

Manufacturing, Oral, Maxillofacial, Orthopedic, Implants, Prosthetics

Provide a brief summary of the potential commercial applications of the research.

Guild foresees the development of this technology as having major impact on hard tissue replacement medicine. The program proposed here is intended to test the feasibility of producing a new class of implantable ceramics with several potential advantages over existing materials and approaches

PRINCIPAL INVESTIGATOR: Mr. Thomas Ward

BUDGET FOR PHASE I DIRECT COSTS ONLY	FROM	TO
	Nov. 1, 1992	February 28, 1993

PERSONNEL (Applicant organization only) NAME	Role on Project	Type of Employment (months)	% Effort on Project	Institutional Base Salary	DOLLAR AMOUNT REQUESTED (omit cents) Salary Requested	Fringe Benefits	TOTALS
Mr. Thomas Ward	PI	0.3	1.0	[redacted]	[redacted]		[redacted]
SUBTOTALS →					[redacted]		[redacted]

CONSULTANT COSTS

Dr. David Fink — [redacted]

EQUIPMENT (Itemize)

SUPPLIES (Itemize by category)

CT/MRI Scanning Services	$3,600	Miscellaneous	$500
Data Manipulation Services	$5,900		
Parts Fabrication Services	$3,500		

[redacted]

TRAVEL
1 trip, Minneapolis, Minn @ $734 — Purpose: Discuss file conversion results.
3 trips, Toledo, Ohio @ $90 — Purpose: Plan and discuss scanning results.

[redacted]

PATIENT CARE COSTS
INPATIENT
OUTPATIENT

CONTRACTUAL COSTS

OTHER EXPENSES (Itemize by category)

TOTAL DIRECT COSTS (Also enter on Page 1, Item 7a)

$ [redacted]

▶ *This figure, when added to the indirect costs, may not exceed $50,000.*

OTHER GRANT AND CONTRACT SUPPORT (See instructions) ☒ NO ☐ YES

OTHER GRANT AND CONTRACT SUPPORT

There are no active or pending projects with any Federal agency which covers the work described in this proposal. A proposal is being considered for submission to the Army's Medical Research and Development Command at Fort Detrick, MD. Planning is in a preliminary phase and the appropriate funding level has not been determined. However, if a proposal is submitted, it will address issues not addressed in the proposal and will compliment, not duplicate the activities described here.

Guild does not currently have any contracts or grants funded by the National Heart, Lung and Blood Institute or any daughter agencies.

BIOGRAPHICAL SKETCHES AND BIBLIOGRAPHY

Thomas J. Ward, P.E.

Present Position: President, Ward Engineering, Inc.

Education: B.S., Mechanical Engineering, The Ohio State University
M.S., Mechanical Engineering, The Ohio State University

Prior Experience

Battelle Memorial Institute, Department of Equipment Development
September 1987–October 1991, Research Engineer

The Ohio State University, Department of Mechanical Engineering
September 1985–September 1987, Research Assistant

Martin Marietta Aerospace, Advance Automation, Denver, CO.
June 1985–September 1985, Engineer

The Ohio State University, Department of Mechanical Engineering
June 1983–June 1985, Research Associate

Relevant Experience:

Technical Direction of Engineering Computer System. Technically directed the advancement of the Battelle Equipment Development Department engineering computer system. This included the purchase and installation of all hardware and software used in the system. Over 90 computers of all different types were included in the system.

Investigation of Computer Scanning Technology. Performed a survey of the vendors in the field of conversion of hand drawn engineering drawings to CAD via scanning technology. Analyzed client needs and prospective vendor capabilities and recommended a system.

Investigation of Rapid Prototyping and Reverse Engineering Technology. Surveyed both the rapid prototyping industry and the three–dimensional scanning industry. Analyzed client needs and prospective vendor capabilities. Quantitatively tested capabilities of prospective systems, and recommended systems for client. The recommended systems were purchased and are in use today.

Integration of Rapid Prototyping Technology into Mechanical Design Process. Used three–dimensional scanning process and SLA process to translate parts in and out of Computer Vision System.

Investigation and Analysis of Surgical Stapler. Simulated and analyzed human tissue models subjected to stapling forces using finite element analysis techniques. Designed and built force transducer internal to stapler. Designed and implemented data acquisition system for experimental studies. Characterized stapling forces in existing stapler design.

Design and Prototype of Endoscopic Surgical Devices. Extensive observation of surgical procedures to determine the best design path to fulfill specific endoscopic needs of a general surgeon. Designed and built multidegree of freedom, electro–mechanical surgical instruments. Design is currently being prepared for testing.

Conceptual Design of Surgical Devices. Observation of surgical procedures to determine the best design path to fulfill specific needs of a general surgeon. Led idea sessions of up to twenty participants. Compiled and analyzed results. Worked directly with market researchers to finalize surgical needs. Designed surgical instrument.

Investigation and Analysis of Industrial Stapler. Simulated and analyzed staple driver model subjected to firing forces using finite element analysis techniques. Designed new driver stop to enhance staple driver life. Experimentally tested new design. New design increased life of stapler by a factor of eight. Redesign implemented for production use.

Design and Manufacture of Robotic Transport Systems for Thermal Spray Technology. Designed and built a two degree of freedom transport system operated in a sealed beryllium spray chamber. Interfaced and programmed controller to operate system. Conceptually designed seven degree of freedom system to be used to spray beryllium mirrors.

Design and Manufacture of Six Degree of Freedom Robotic Hand Controller. Designed and built a six degree of freedom hand controller to be used to control a dual arm manipulator system. The design is specific to the right hand, anthropometrically correct, comfortable for very long periods of use, yet compact. Client has since ordered another controller for the left hand. Both controllers are being used full time in the field.

Design of Robot Wrist. Designed four degree of freedom robot wrist for a high performance, seven degree of freedom manipulator. Work included extensive nonlinear finite element analysis (MSC/NASTRAN) of critical components.

Investigation and Implementation of Teleoperation Force Feedback System. Investigated, designed, and implemented power and sensing systems of a force feedback system for a dual arm, teleoperation system. Designed a cable based power system for a six degree of freedom hand controller.

Design of a Precious Metal Filter for Hydrogen Liberation in Arctic Pipeline Cooling Towers. Designed a spherical shaped palladium–silver filter that is to be used to liberate excess hydrogen from arctic heat pipes. Manufactured prototypes and experimentally tested proof pressure of design.

Experimental Verification of Filtration Characteristics of Palladium–Silver Filter. Worked with team of corrosion and catalyst scientists to experimentally verify filtration characteristics of palladium–silver filter. Effort included the design and manufacture of test apparatus, performance of tests, and analysis of test results. This is an ongoing effort.

Engineering Design, Analysis and Drawing Preparation of Plastic Consumer Products. Worked with an industrial design firm to bring to market a set of plastic injection molded consumer products that were subjected to high consumer forces and abuse. These products will replace the client s current metal products. Engineered the industrial design firm s design so that the part was manufacturable and able to withstand long–term consumer use. Interpreted and directed FEM analysis of engineering design. Prepared manufacturing quality drawing set for manufacturing firm.

Analysis and Design of Medical Processing Equipment. Developed sensor suite and data acquisition system needed to investigate and analyze medical processing equipment failures. Used generated data to pinpoint problem areas in design. Redesigned and retrofitted design changes to existing equipment. The retrofitted equipment produces four times faster than previously and is currently being used in production.

Professional Affiliations

Member of American Society of Mechanical Engineers,; American Society of Metals

Licensed Professional Engineer in the State of Ohio

David J. Fink

Present Position: President, Bio–Integration, Inc.; President, CollaTek, Inc;
Primary Consultant, Guild Associates, Inc.

Education
B.S.Ch.E — 1966 — University of Cincinnati (Chemical Engineering)
M.S.E. — 1967 — University of Michigan (Chemical Engineering)
Ph.D. — 1973 — University of Michigan (Chemical Engineering)

Relevant Experience:

CollaTek, Incorporated **EIN: 22–2872840**

CollaTek, Inc. was founded by Dr. Fink and Gattefosse SA of Lyon, France, in order to develop and commercialize a novel processing technology for manufacturing medical implant devices from biopolymers, including collagen-based prosthetic devices. Through CollaTek, Dr. Fink has developed an active collaboration with the Skeletal Research Center at the Case Western Reserve University in Cleveland, OH, where he is also an Adjunct Assistant Professor of Biology. He is currently consulting at CWRU on a major project to investigate the mechanisms of biomineralization and development of biomimetic ceramic processes.

Bio–Integration, Incorporated **EIN: 31–1162326**

In January, 1986, Dr. Fink founded Bio–Integraton, Inc., a consulting company working in the biotechnology/ biomedical products, other than collagen.

Bio–Integration clients have included:

American (Baxter) Dade Chemistry Systems, Miami, FL
Battelle Memorial Institute, Columbus, OH
The Boston Consulting Group, Boston, MA
Case Western Reserve University, Cleveland, OH
Electro–Nuclonics, Inc., Fairfield, NJ
Fisher Scientific, Pittsburgh, PA
Guild Associates, Columbus, OH

Battelle, Columbus Division

505 King Avenue, Columbus, Ohio 43201

Associate Section Manager — 1983 to 1985; Projects Manager — 1981 to 1983
Principal Research Scientist — 1977 to 1981; Staff Scientist — 1974 to 1977

While at Battelle, Dr. Fink participated in over 100 research projects, and was Principal Investigator for over 25 of these. From 1983 to 1985, he was an Associate Section Manager at Battelle's Columbus Division, with responsibilities for directing a group of 8–15 researchers in areas involving applied biochemistry and medical technology. Duties in this role included planning and coordination of project development, proposal preparation, project management and review, and personnel recruiting and management. Major programs included:

- Program Manager and Co–Investigator of a series of projects to investigate the properties and applications of oriented collagen biomaterials, with internal funding by Battelle and from external industrial sponsors.
- Co–Investigator of a $5.5 million/5–year grant from the National Institutes of Health, Division of Research Resources, to establish the National Center for Biomedical Infrared Spectroscopy, for which he served as Coordinator of Collaborative Research and Director of Core Research.
- Principal Investigator for seven years for a classified government project, which exceeded $2.3 million in funding.

Research & Development Interests

Enzyme technology — industrial, clinical, and analytical applications
Immunological methods in analytical biochemistry
Controlled–release drug delivery devices
Microencapsulation and related membrane processes
Collagen fibrillogensis and biomaterials
Preparation and characterization of non–thrombogenic materials
Biomedical applications of Fourier transform infrared spectroscopy
Applications of fractal geometry

Membership

American Institute of Chemical Engineers
Controlled Release Society
Society for Biomaterials
Cobientz Society
Society for Applied Spectroscopy

Selected Publications

Kjellstrand, C., H. Borges, C. Pru, D. Gardner, and D. Fink. 1981. The Clinical Use of Microencapsulated Zirconium Phosphate–Urease for the Treatment of Chronic Uremia, Transactions of the American Society for Artificial Internal Organs, pp. 24–30.

Jakobsen, R.J., L.L. Brown, S. Winters, T.B. Hutson, D.J. Fink, and A. Veis. 1981. Intermolecular Interactions in Collagen Self Assembly Revealed By Fourier Transform Infrared Spectroscopy. Science, 220: 1288–1290.

Hughes, K.E., D.J. Fink, T.B. Hutson, and A. Veis. 1983. Oriented Fibrillar Collagen and its Application to Biomedical Devices. Journal of the American Leather Chemists Association, 79: 146–155.

Gardner, D.L., C.M. Kjellstrand, C.R. Hassler, D.J. Fink and D.C. Emmerling. 1984. An Orally Administered Microcapsule System for Treating Chronic Renal Failure Patients. Applied Biochemistry and Biotechnolgy, 10: 27.

Alberti, J.C., J.A. Phillips, D.J. Fink and F.M. Wasacz. 1985. Off–Line Monitoring of Fermentation Samples by FT–IR/ATR: A Feasibility Study for Real–Time Process Control. Biotechnolgy and Bioengineering, Symposium Series No. 15, 689–722.

Chittur, K.K., D.J. Fink, R.I. Leininger and T.B. Hutson. 1986. FT–IR Studies of Protein Adsorption in Flowing Systems. Approaches for Bulk Correction and Compositional Analysis of Adsorbed and Bulk Proteins in Mixtures. Journal of Colloid and Interface Science, 111: 419–433.

Fink, D. J. and K. K. Chittur. 1986. Monitoring Biological Processes by Fourier Transform Infrared Spectroscopy. Enzyme and Microbial Technology, 8: 568–572.

Chittur, K.K., D.J. Fink, T.B. Hutson, R.M. Gendreau, R.J. Jakobsen and R.I. Leininger. 1987. FT–IR/ATR Studies of Protein Adsorption in Flowing Systems. Chapter 23 in Proteins at Interfaces: Physicochemical and Biochemical Studies. Ed. by J.L. Brash and T.A. Horbett. ACS Symposium Series No. 343, 362–377.

Hughes, K.E., D.J. Fink, T.B. Hutson, and A. Veis. 1988. High–Strength Collagen Biomaterials. Journal of the American Leather Chemists Association. 83: 372–377.

Nakamura, O., D.J. Fink and Arnold I. Caplan. 1991. Oriented Collagen Matrices: The Control of Biomineralization in Bone. In Materials Synthesis Based On Biological Processes, Ed. by M. Alper, P. Calvert, R. Frankel, P. Rieke and D. Tirrell. Materials Research Society Symposium Proceedings, Vol. 218: 275–280.

Heuer, A.H., D.J. Fink, V.J. Laraia, J.L. Arias, P.D. Calvert, K. Kendall, G.L. Messing, P.C. Rieke, D.H. Thompson, A.P. Wheeler, A. Veis and A.I. Caplan. 1992. Innovative Materials Processing Strategies: A Biomimetic Approach. Science, 255, 1098–1105..

Wu, T–M,D. J. Fink, J L Arias, J P Rodriguez, A H Heuer, and A I Caplan; 1992. "The Molecular Control of Avian Eggshell Mineralization", Proceedings of the 3rd International Conference on the Chemistry and Biochemistry of Mineralized Tissues, in press.

Nakamura, O., D.J. Fink, V.L. Laraia, A.H. Heuer and A.I. Caplan. Matrix–directed In Vitro Osteogenesis. Manuscript submitted.

Salvatore T. DiNovo

Present Position: President, Guild Associates, Inc.

Education: BSChE, University of Dayton, 1964
MSChE, State University of New York at Buffalo, 1972

Relevant Experience:
Mr. DiNovo is a Registered Engineer in Ohio, No. E– 043245.

Mr. DiNovo brings equipment development experience which spans the gamut between application research through design and production. This base includes participation in the commercial introduction of separation technologies with special emphasis on its application to gas separation.

In 1981, sensing the need and opportunity for small, high performance technology-based companies, Mr. DiNovo formed Guild Associates, Inc. Virtually since its first year in existence, Guild has taken an active role in adapting advanced technological systems to military needs. These activities have focused strongly in military medicine. For example, Guild conducted a major, multi–year development activity which has led to fielding of a self-contained oxygen generation system for use at Army field hospitals. Using advanced electronic systems, this system is capable of sensing and adjusting its operation to the climatic condition extant at the operational site. Mr. DiNovo served as Program Manager on this multi–million dollar project.

Mr. DiNovo has also led two HHS–funded SBIR projects. The first, awarded in 1983, was based upon developing an advanced fluid separation concept for use as a wearable artificial kidney. More recently (1989), Guild was awarded a project to examine the use of neural network architecture to unique problems experienced by developmentally disabled individuals.

Earlier at Union Carbide, Mr. DiNovo had served with distinction in the design group responsible for commercialization of PSA technology throughout the Chemical Industry. The first commercial PSA units produced high purity (99.999+% by volume) hydrogen, and Mr. DiNovo was the lead process engineer in several key projects, including the system which was, for almost five years, the largest PSA unit operating in the world. He also was chosen as Union Carbide's emissary to Japan, and was the first individual to operate a commercial–scale gas separation PSA unit in that country.

In late 1972, Mr. DiNovo was offered a position at Battelle Memorial Institute's Columbus Laboratories with much broader responsibilities. During the seventies, he held numerous line and project management responsibilities at Battelle. During this period, he maintained a small, close–knit group of engineers and scientists specializing in separation technology.

RESEARCH PLAN

FREE FORM MANUFACTURING OF MEDICAL DEVICES

Guild Associates has identified a strategy for a new manufacturing approach that will provide customized prosthetic devices for hard tissue reconstruction. Guild proposes that Free–Form Manufacturing (FFM) technology may represent a valuable new tool for making implants that reproduce original tissue size and shape, and that maximize the rate of cell–mediated hard tissue healing. The Guild concept requires integration of several independently developing technologies into the FFM system.

This strategy for reconstruction of traumatic, disease–related or surgical loss of hard tissue is based on the hypothesis that therapy will be optimally treated by a prosthesis that:

1. is matched to the precise anatomical dimensions of the original tissue (or that may be modified to compensate for anticipated healing responses or to provide for surgical-assist structures);

2. is composed of a ceramic material that exhibits properties similar to bone, and that presents physical, chemical and surface properties that facilitate bone cell function and production of new bone;

3. is designed to maximize the rate of cellular colonization of the ceramic matrix and to direct the production of new bone — alternatively, a more active approach is to optimize the device for seeding by autologous cells derived from the patient.

Manufacturing steps in the process will include:

1. specification of the physical properties of the customized prosthetic device by use of available computerized imaging techniques (for example, Computerized Tomography, CT, or Magnetic Resonance Imaging, MRI) to produce a solid model "design file". This specification may also involve secondary manipulation of the files to assist in surgical implantation and/or to compensate for, or optimize, anticipated healing processes;

2. development of a mathematically processed design file to produce a "sliced file" suitable for directing an FFM process;

3. construction of a precise replica of the sliced file by FFM in an appropriate ceramic material to produce the implant.

The overall objective of this program, therefore, is the development of an integrated system for imaging hard tissue, manipulating the image file to produce the design file, processing the design file to drive the FFM system and produce the implant, and optimizing the surgical implantation and performance of such devices. Guild Associates' goal is to develop a new method for fabricating customized medical implant devices by serving as the focus for integrating component technologies. It is anticipated that this technology will then be offered to the general orthopedic and dental communities as a specialized service.

A. Specific Aims

As the first steps toward the development of an integrated system to produce customized hard tissue implants, Guild Associates proposes to conduct a Phase–1 project to achieve the following goals:

1. Demonstrate the feasibility of converting CT images to FFM protocols, including investigation of the "segmentation" problem involved in isolating the target hard tissue from surrounding tissue fields in the imaging file;

2. Compare the performance of alternative FFM vendors and technologies;

3. Select and approach the best vendor for collaboration in the Phase 2 project.

B. Significance

Background

Ceramic implants

It has been only slightly more than two decades since the discovery by Hench and his co-workers [1] that a direct chemical bond can form between certain "bioactive" glass–ceramic materials and bone, thereby potentially stabilizing dental or orthopaedic implants made from these materials. In the meantime, the investigation of other chemical formulations (including many ceramics and composities), physical forms (e.g., dense or porous particulates and solids, coatings, and composites), and clinical applications have progressed rapidly [2,3].

Most research into the use of bioactive materials is now focused on either

1. glasses or glass–ceramic, primarily compositions from the SiO_2–P_2O_5–CaO–Na_2O system [4], or
2. calcium phosphate compositions, primarily β–tricalcium phosphates (β–TCP), $Ca_3(PO_4)_2$ and calcium hydroxylapatite (HA), $Ca_{10}(PO_4)_6(OH)_2$, and combinations of the two [5,6].

Generally, the calcium phosphate ceramics may be somewhat easier to produce and/or obtain commercially, and are receiving an increasing share of the research and clinical attention [3,4]. β–TCP is normally observed to biodegrade much more rapidly than HA, which until recently was believed to be non–resorbable [7,8]. Such bioactive ceramics are generally considered to be *osteoconductive* (i.e., providing an appropriate scaffold that permits ingrowth of vasculature and osteoprogenitor cells), as opposed to *osteoinductive*, which implies a more active process in which the matrix recruits osteoprogenitor cells from the local tissue or circulation [5].

A recent workshop, convened to assess the status and requirements of calcium phosphate ceramics as implant materials, identified current or potential applications for these materials[7]:

Dental and other head and neck uses [9]

Craniofacial Applications
- Augmentation — Ridge; Mandibular; Zygomatic; Chin
- Reconstruction— Peridontal; Mandibular; Orthognathy; Bone Grafting; Cranioplasty; Orbital floor; Anterior nasal spine

Prosthetic Implants
- Subperiosteal
- Endosteal — Endosseous implants; Endodontic pins; Orthodontic pins
- Transosseous — Transmandibular

Otological Applications
- Ossicular reconstruction
- Canal wall prostheses

Orthopedic Uses [10]

Bone Graft Substitutes
Augmentation — Delayed or failed unions; Arthrodesis (fusion of joint);
Bone graft donor sites; Mechanically stable cystic defects;
Revision or primary joint replacement
Replacement — Vertebral body defects; Segmental bone defects;
Mechanically unstable subchondral defects (e.g., tibial plateau fractures and large traumatic defects; Grafting around prostheses used for mechanical fixation

Fracture Fixation Materials
Fracture fixation devices such as plates, screws and rods;
Endoprosthese such as joint replacements

Coating for Fixation
Fixation of implant to bone in joint replacement;
Coated internal fixation devices

Drug Delivery Implants
Local adjuvant chemotherapy; Local antibiotic therapy;
Local delivery of bone growth factors or osteoinductive factors

HA, the predominant ceramic in bone, and the composition of the bond between bioactive ceramics and bone, has been assessed to provide the following advantages in dental implantations [5,11]: 1. biocompatibility; 2. absence of antigenic response; 3. availability; 4. ability to use local anesthesia during implantation; 5. low risk of infection; 6. low risk of permanent hyperesthesia; 7. lack of significant resorption; 8. high rate of good results; and 9. no need for perfect oral hygiene on the part of the patient. Most of these advantages can be anticipated in orthopedic applications as well, although the need for a more rapid rate of resorption has been the incentive for investigation of mixtures of HA and β–TCP to produce a range of rates [5].

For use in these applications, calcium phosphate materials are currently produced in a variety of formats, normally by sintering particulate solids [12]:

Particulates — range of particle sizes; variable porosity

Moldable Forms — pastes; self–setting slurries or preformed shapes

Block Forms — designed geometries such as rods, cones, spheres, and discs; variable micro– and macroporosity

Coatings — applied to a preformed substrate by techniques such as plasma spraying, flame spraying, electrophoresis, ion beam–radio frequency sputtering, dip coating, and frit–slurry enameling

Particulate formats were among the first bioactive ceramics taken to the clinic, but these materials have the disadvantages 1) they cannot be used where implant strength is required and 2) particle migration often occurs in the implant site, decreasing the effectiveness of the material [5]. To minimize the latter problem, many attempts have been made to use biodegradable materials to agglomerate and mold the particles during implantation [5].

In clinical applications in which strength of the ceramic implant is a significant factor (e.g., craniofacial augmentation or reconstruction; bone replacement; fracture fixation), block forms of the material are required and shaping of the implant becomes more difficult.

Perhaps the most important physical properties of bioactive ceramics are the volume and size of the pores within the material, which strongly influences both the tensile and compressive strengths of the material and the rate of resorption and cellular colonization [12,13]. Generally, pores at least 200–300 micrometers in diameter (referred to as macroporosity) are believed to be necessary in osteoconductive materials to permit ingrowth of vasculature and osteogenic cells. Microporous ceramics, on the other hand, with pores only a few micrometers in diameter, do not permit cellular invasion, and in most cases, are likely to be more difficult to stabilize in the implant site [5]. An example of an implant material selected for its consistent macroporosity is the "replamineform" calcium phosphate structures derived by chemically transforming a variety of corals (initially calcium carbonate), which are composed of a network of interconnecting pores in the range of approximately 200 μm diameter [14]. HA materials of this type are marketed by Interpore Orthopedics, Inc. of Irvine, CA.

An alternative approach to the fabrication of customized ceramic implants, involving a CT–integrated computerized milling operation to produce molds or implants, has been clinically tested for facial reconstruction [15]. Advantages of this prefabricated implant approach were identified as [5]:

1. Contour (of facial implants) is to the underlying bone base (as opposed to the surface of the skin by standard facial moulage techniques);
2. Formamina are localized (implants are designed to avoid nerve foramina);
3. Covered areas are "visible" (no interference in the design from hair or dressings);
4. Soft–tissue contours can be evaluated;
5. Pre–existing implants can be evaluated;
6. Volume measurements can be obtained;
7. Local anatomy can be better visualized;
8. Models are provided for "practice surgery";
9. Templates can be designed for bone graft surgery;
10. An archive can be maintained for clinical re–evaluation and academic study;
11. Prefabricated grafts minimize the time for implant sculpting in surgery, while the patient is anesthetized, and generally are much more accurate reconstructions of the desired bone than can be accomplished by hand;
12. There is no need for a second surgical site, as in autogenous graft surgery.

In the CT–integrated milling operation described, implants can be made directly by milling the solid ceramic, or by preparing a "negative" mold of the implant, then molding the implant using a

formable ceramic composition [15]. Direct milling is difficult with macroporous bioceramics, including the coralline HA materials. A moldable HA–collagen composite material has, therefore, been clinically tested with good results in low–strength indications. However, the composite is relatively friable, loses strength when moistened, and not suitable where structural strength is required, for example, for long bone or mandibular reconstructions [15]. In addition, control of implant macroporosity is a significant constraint when using the composite molding technique.

Free–Form Manufacturing

The terms free–form manufacturing (FFM), desktop manufacturing, rapid prototyping, and several others, all describe the new manufacturing processes that enable the physical fabrication of three–dimensional computer models with a minimum of human interaction[16]. All of the systems that are on the market or in development are based upon mathematically "slicing" a three dimensional Computer Aided Design (CAD) model and then sequentially reconstructing the cross sections (slices) of the model on top of one another using the manufacturing system's solid medium.

The proven, largest commercial supplier of FFM systems, 3–D Systems (Valencia, CA), markets a "stereolithography" system based upon laser–mediated polymerization of photo–sensitive liquid monomer. It had commercial sales of over $24 million in 1990, with an impressive customer list[17]. All other competitive companies combined have sold only a handful of units. 3–D Systems began providing commercial units in 1987, while most other vendors have been selling equipment only since 1990, and none of the competitors is well established in the market place [18].

Of the FFM processes, only two are able to work with ceramics: the "Selective Laser Sintering"[19,20] system marketed by DTM Corporation (Austin, TX) and the "3 Dimensional Printing" system under development at the Massachusetts Institute Technology (Cambridge, MA)[21]. Both processes can accept the industry standard STL file format, and both research organizations are working with industry to commercialize their respective processes.

The DTM process is based upon localized sintering of powder material by a scanning laser beam [22]. When the laser beam impinges on the surface powder, it melts, and localized bonding between particles take place. By selectively sintering sequential layers, the shape is built in a manner of hours. The build rate depends on the complexity and size of the part, power output of the laser, the coupling between the laser and the material and the rheological properties of the material. [22]

Although DTM markets only polymer–based manufacturing at this time, it is currently in the research phase of developing ceramic capabilities. To date, fabrication of ceramics, including alumina/phosphate composites, have been demonstrated in the DTM process.

The MIT process, which has not been commercialized yet, is based upon selective binding of a powder, using ink–jet techniques to distribute the binding agent, as illustrated schematically in Figure 1. Typical devices are built from alumina powder bonded with colloidal silica, to reproduce a typical ceramic shell.

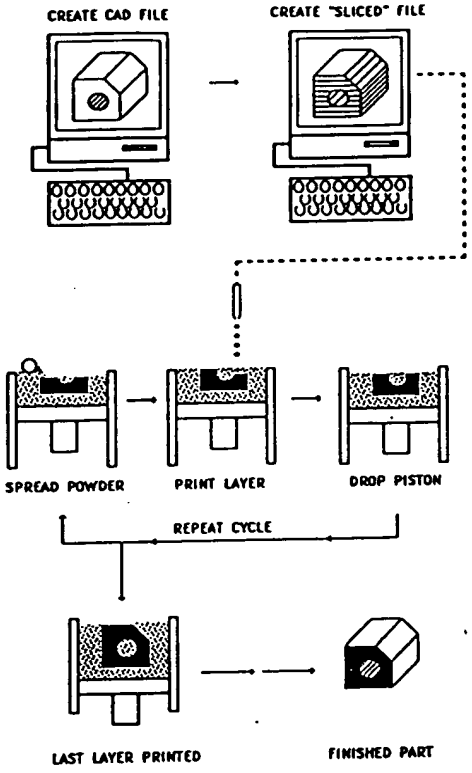


FIGURE 1. SCHEMATIC FOR MIT "3–D PRINTING" PROCESS

Unique ceramic processing may be required for each specific approach. In the $Al_2O_3/NH_4H_2PO_4$ system for example, alumina has a melting point of 2045°C while $NH_4H_2PO_4$ has a melting point of 190°C. Crystalline materials like ammonium phosphate and boron oxide show a definite melting point which the viscosity drops sharply. When the alumina/ammonium phosphate blend is processed with the DTM laser, the lower–melting–point phosphate melts to form a glassy material and bonds the alumina particles. A secondary heat treatment is necessary to develop the full strength of the material. During heat treatment at 850°C, the following net reaction takes place.

$$Al_2O_3 + 2NH_4H_2PO_4 \text{ (glassy)} \rightarrow 2\,AlPO_4 + 2NH_3(g) + 2H_2O(g)$$

The reaction results in an $Al_2O_3/AlPO_4$ composite where aluminum phosphate forms a thin layer around the alumina particles. The $AlPO_4$ volume fraction depends on the initial composition [22].

Guild anticipates that FFM technology may present a unique capability to introduce a defined porosity into ceramic devices formed by aggregation (sintering) of particulate substrates. For example, the porosity might be introduced or modified: 1. by direct reproduction of a "porous" CT file; 2. by varying the particle size distribution of the base ceramic; or 3. by post-treatment of formed devices to remove specific agents included in the original mixed–particulate bed (e.g., by differential solubility). These processes offer a range of porosities available to tailor FFM devices to specific applications. Considerations of this type will not be investigated until the second phase.

CT Imaging

In 1979 Houndsfield and Cormack were awarded the Nobel Prize in Medicine for their contributions to Computed Tomography (CT). Since then virtually every major hospital in the world has acquired the ability to perform CT. As opposed to classical x–ray imagining, where a shadow image of a patient volume is created, CT is a two step process where 1) the patient is imaged at multiple angles through the rotation of an x–ray source, and 2) the image is manipulated in the computer to create a series of sliced images of the patient. Through the use of sophisticated computer algorithms, the sliced information can be reconstructed to form three dimensional images of the patient's tissue.

A complexity of the manipulation process to create the FFM design file is the isolation of the specific tissue of interest from the surrounding tissue, a process (often relatively subjective) termed "segmentation". This selection process can be based upon matching grey–scale intensities directly from the CT file without operator interaction. [23]

In the CT process each volume pixel (voxel) in a patient cross section is assigned a CT number (in Houndsfield units) based upon the physical density of the material with respect to water. These numbers are stored in 256 X 256 or 512 X 512 square array format. This information is manipulated in the computer to show corresponding grey or color scales for selected tissue on the computer display. This array–formatted information can also be transferred from the CT scanner into graphic engineering computers for subsequent data manipulation as demonstrated, for example, by Kaplan in the development of the integrated ceramic milling system [15].

Preliminary investigations, at the Medical College of Ohio for example, have also demonstrated that relatively crude FFM models of complex anatomical structures can be prepared from MRI image files by the stereolithography system from 3–D Systems[25].

Commercial opportunities

The FFM program proposed here will test the feasibility of producing an implantable calcium phosphate ceramics with the potential advantages over existing materials and approaches of:

1. customization of implant devices directly from CT/MRI records and with design improvements added to image file
2. production of improved ceramic implants with greater complexity in shape and controlled macroporosity
3. minimization of particle migration observed in particulate formats
4. no milling of the final device—the final shape is produced directly by the FFM process.

Research Requirements

Guild Associates recognizes that the overall objectives of this program will involve the consideration of many complex technical issues and the integration of a diverse group of scientific

specialties. For the purposes of developing an integrated FFM technology for customized ceramic implant production, these issues have been prioritized as follows:

1. CT or MR image processing — convert image files to solid model CAD files, which includes the "segmentation" problem of isolating the "hard tissue" database from surrounding tissue in the image field.
2. FFM technology — compare processing needs from competitive vendors and identification of potential strategies for ceramic device production.
3. Ceramic materials — characterize, then optimize for
   - control of chemistry (e.g., HA/β–TCP ratio; ionic substitutions)
   - control of physical properties (e.g., micro– and macroporosity, interconnectivity of pores, and surface area)
   - mechanical properties of ceramic materials and FFM devices (e.g., stiffness, tensile and compressive strengths, and hardness)
4. Biocompatibility of ceramic material — in vitro and in vivo testing of standardized compositions, shapes and porosities
   - characterization of cellular responses to the materials
   - determination of rate and mechanism(s) of resorption
   - characterization of osteoconductivity, bone formation and matrix remodeling
5. Implantation of FFM devices in appropriate animal models
6. Modification of the imaging technique and implant design file to
   - assist in implantability of devices
   - compensate for anticipated neo–bone formation and device resorption
   - enhancement of resolution of the imaging process

The Phase–1 program proposed here is intended to test feasibility of the first step in this development process, namely the conversion CT image files to FFM devices. It is anticipated that significant additional research and development (in the Phase 2 program and beyond) will be needed to demonstrate the utility of the FFM approach, confirm the biocompatibility of materials produced and the performance of implants, and to commercialize the FFM process.

Relevant Experience

The critical experience base needed to successfully complete proposed effort reside in Mr. Ward and Dr. Fink. Their resumes have been purposefully expanded to convey the significant resource their experience represents.

Guild, as a company, has been active in biomedical equipment, primarily through a long contract association with the Medical Research and Development Command at Fort Detrick, MD. These

efforts primarily involve oxygen generation equipment, for which Guild has obtained a 510K from FDA. Guild is familiar to a limited extent with the issues involved in obtaining approval for devices. It is unlikely that this will become relevant in Phases I and II, but could come into play in Phase III.

As indicated in the Research Requirements section and elsewhere, the current project is one segment of a multi–faceted effort that must be completed if the technology described in this proposal is to reach its commercial potential. To this end, Guild has established contacts with and received expressions of interests from other well–known technical specialists. If a Phase II project is proposed, it is likely these individuals may play important roles. Furthermore, as the project unfolds, the emphasis between computer–related research (represented by Mr. Ward's activities) and biomedical issues (Dr. Fink's expertise) will change. As in the Phase I effort, Guild believes the Principle Investigator position should reflect the importance of a discipline in the suite of problems addressed during a grant period. Depending on the next logical sequence of steps in Phase II, either of these researcher leaders may serve as PI or they may share that role.

Experimental Design and Methods

Technical Plan Discussion

As demonstrated above, the transformation of a CT bone image to a polymeric FFM reproduction is a feasible task. Guild's proposed approach for demonstrating this capability, and testing the fabrication of ceramic devices is outlined in Figure 2. The following is a step–by–step discussion of the proposed process anticipated problems and concerns and specific solutions and recommendations to each.

Guild believes that the key aspects of this research are the segmentation process, in which the "bone" is recognized and separated from the other tissues in the image, and the reproduction of a smooth bone surface, which entails the manipulation of the data after segmentation. Four iterations of the process are planned with each successive run being more difficult than the last in both the recognition of bone and the reproduction of the bone.

During the first iteration process, the specimen will be approximately 1 inch of the mid section of a canine femur. This simple bone section is used because it has minimal surface features and the perimeter of the bone is well defined and easily recognizable during the transformation process. It is expected that a minimum number of scans (10 – 20) can be used.

During the second iteration process, the distal end of a canine femur, with the tendons, ligaments and cartilage still attached to it, will be imaged. The purpose of this test is to recognize the bone from the surrounding soft tissue, and to form a smooth, accurate bone end from the CT data. The presence of the articular and fossa surfaces, along with the attached soft tissue will increase the complexity of this iteration over the first. This will be the first test of the segmentation process.

During the third iteration, a non–dissected canine hindleg will be imaged. The propose of this test is to segment the bone completely from the surrounding tissue and adjoining bones. The presence of

adjoining bones, cartilage, and attached tendon and muscle will increase the complexity of this recognition process over the second. The data files will also grow dramatically due to the increased volume of the CT scan data.

During the fourth iteration, the imaged information from one of the previous iterations (preferably the third) will be reproduced in a ceramic material. This bone reproduction will then be quantitatively compared to both the original and the polymer reproductions. The purpose of this test is to demonstrate the feasibilty of ceramic implant manufacture by FFM techniques.

Process Discussion

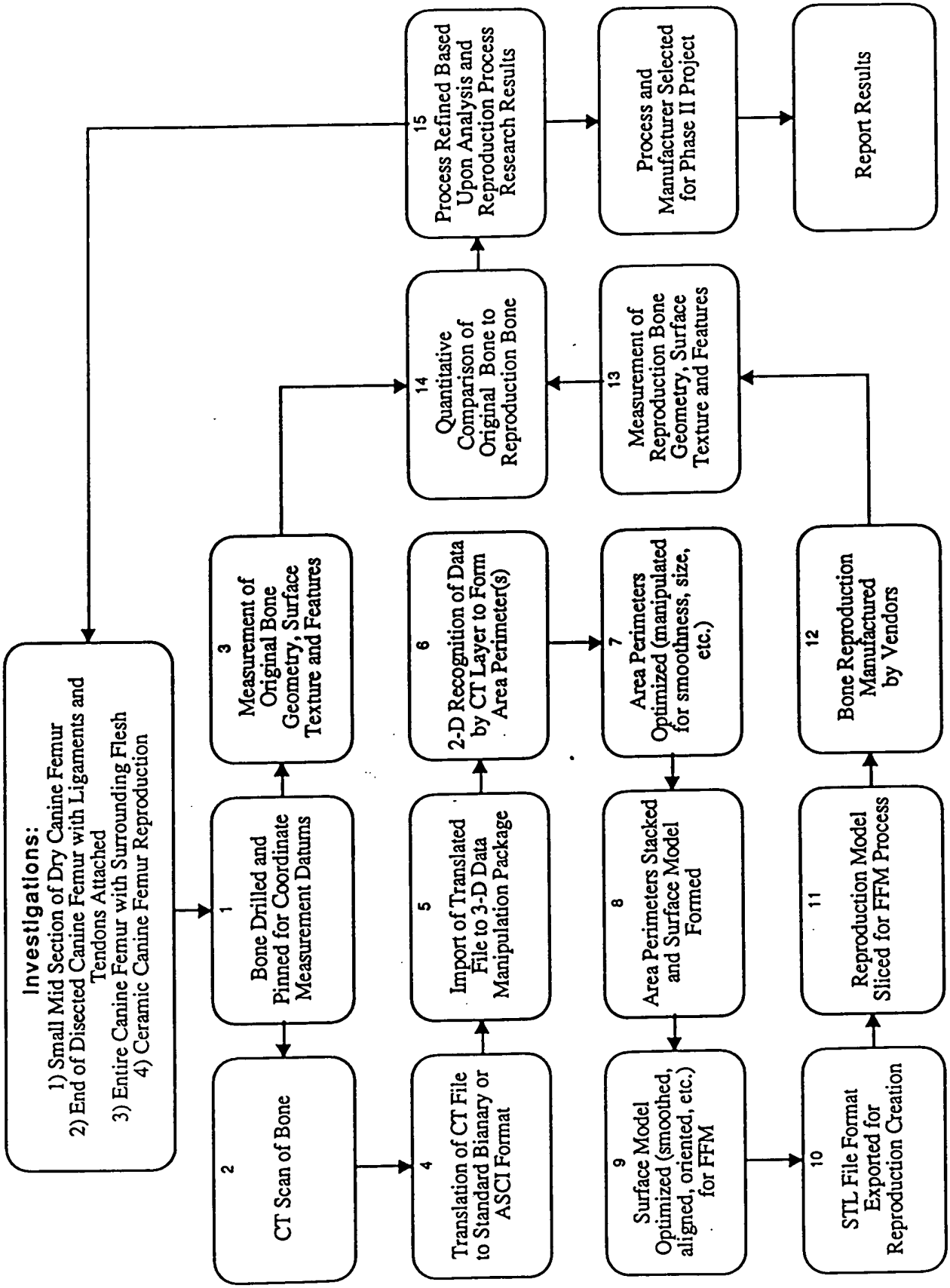
During the first two iterations, the bone will be prepared by drilling and reaming two 0.125–inch holes that are mutually orthogonal. These holes will serve as reference datums for quantitative measurement.

The bone will be scanned at a CT scan line distance of 1 to 2 mm. The normal of the scan sections will be parallel to the bone axis. The output of the CT scanner will be 512 by 512 arrays of 16-bit grey scale data. The CT data will be translated to a TIF format using previously developed code. The TIF formatted file will be imported to DataSculpt®, a three–dimensional data manipulation package, which will be used to process the CT data. This software runs on a Silicone Graphics Personal Iris computer.

Internal to the data manipulation package each scan will be manipulated so that the perimeters of the solid areas of the bone are defined. This process will be performed using both DataSculpt® and application–specific code. DataSculpt® is able to recognize the grey scale information and draw perimeter splines about the information. After the perimeterization is complete the perimeters will be manipulated to decrease the amount of data to be processed, while maintaining the integrity of the data. At this point the amount of data will be at least two magnitudes smaller than received from the CT scan.

The area perimeters will be rejoined to form a wire frame of the bone. At this point the data spline points will be aligned to prevent aliasing the surface of the model, and the resolution of the model will be determined. During the first run we anticipate that resolution will be in the 20—50 mil range. In subsequent runs we expect to be able to converge on FFM resolution of 5 mils. Computer processing speed and disk space can become critical during this process.

Figure 2. Transformation of Bone CT Scan Data to an FFM Reproduction



If a satisfactory final resolution can not be reasonably made due, to exorbitant processing times, then an additional small part will be manufactured to the high resolution, while the other models are reproduced to a lower resolution.

A surface model composed of triangles will be made from the wire frame data, then translated to STL format for FFM. This data will be sent to the vendors (eg. DTM corporation in Austin, Texas) for prototyping. It is expected that four units of each model will be reproduced.

During the first two iterations the scanned bone will be quantitatively measured using the holes drilled as datums. Surface texture will be measured for the different areas on the bone surface. When the models are returned from the FFM vendors, they will be measured and compared to the original bone.

Depending on the results of each iteration, the subsequent iteration procedures will be modified. All major problems will be resolved during a given iteration before the following iteration takes is undertaken.

An important element of the Phase–1 project will be the evaluation of competitive technologies and the development of collaborative relationships during these interactions. Guild anticipates that selection of a formal collaborative venture (or perhaps acquisition of a single vendor's system, for its own account) will be made before a Phase–2 grant application is submitted, if appropriate.

Human Subjects

The project team will not require the participation of human subjects in Phase I and does not anticipate their use in Phase II.

Vertebrae Animals

The project team will not require the participation of vertebrae animals in Phase I. Vertebrae animals may be used in Phase II if the results from Phase I research warrant. It is anticipated that canine femur specimens will be acquired from animals sacrificed at The Ohio State University School of Veterinary Medicine, from approved investigation not involving these tissues.

Consultants

Both Dr. Fink and Mr. Ward currently are employed by other firms. The letters are attached in the Appendix.

Contractural Arrangements

The arrangement and referenced documents mentioned in the previous paragraph constitute the only agreements made for undertaking this project.

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CHECKLIST

This is the required last page of the application.

(Check the appropriate boxes and provide the information requested.)

TYPE OF APPLICATION

[X] NEW application *(This application is being submitted to the PHS for the first time.)*

[ ] REVISION of previously-submitted application no. _____
(This application replaces a prior unfunded version of a new application.)

[ ] Change of Principal Investigator *(if applicable)*
Name of former Principal Investigator _____

1. ASSURANCES/CERTIFICATIONS

The following assurances/certifications are made by checking the appropriate boxes and are verified by the signature of the CORPORATE OFFICIAL on the FACE PAGE of the application. See APPENDIX, beginning at Page i, for descriptions of individual assurances/certifications.

a. Human Subjects *(Complete Item 4 on the Face Page)* [ ] Full IRB Review [ ] Expedited Review

b. Vertebrate Animals *(Complete Item 5 on the Face Page)*

c. Debarment and Suspension
[X] No [ ] Yes *(Attach explanation)*

d. Drug-Free Workplace
[X] Yes [ ] No *(Attach explanation)*

e. Delinquent Federal Debt
[X] No [ ] Yes *(Attach explanation)*

f. Misconduct in Science (Form PHS 6315) [ ] Filed [X] Not Filed If filed, date of Initial Assurance or latest Annual Report: _____

g. Civil Rights *(Form HHS 441)*
[X] Filed
[ ] Not Filed

h. Handicapped Individuals *(Form HHS 641)*
[X] Filed
[ ] Not Filed

i. Age Discrimination *(Form HHS 680)*
[ ] Filed
[X] Not Filed

2. PROGRAM INCOME *(See APPENDIX, Page xii.)*

All applications must indicate (Yes or No) whether program income is anticipated during the period(s) for which grant support is requested.

[X] No [ ] Yes *(If "Yes," use the format below to reflect the amount and source(s) of anticipated program income.)*

Budget Period	Anticipated Amount	Source(s)

INDIRECT COSTS

Insert the rate, if known. If the applicant organization does not have a currently negotiated rate with the DHHS or another Federal agency, it must estimate the amount of indirect costs allocable (applicable) to the proposed Phase I project. That amount should be inserted in the space provided below. The applicant organization should also be prepared to furnish financial documentation to support the estimated amount, if requested by the PHS. An applicant organization may elect to waive indirect costs if it so desires. Further information on indirect costs is available from: Chief, Financial Advisory Services Branch, Division of Contracts and Grants, National Institutes of Health, Building 31, Room 1B43, Bethesda, Maryland 20892; (301) 496-2444. [redacted] /Direct Labor Hour – Indirect of Total Direct & Indirect – G&A

[X] DHHS agreement, dated: December 19, 1988; _____ % salary and wages or _____ % Total Direct Costs.

[ ] No DHHS agreement, but rate established with _____, dated: _____

[ ] Rate negotiation pending wth the National Institutes of Health, Financial Advisory Services Branch.

[ ] Indirect costs allocable (applicable) to this Phase I project are estimated to be $ [redacted]

[ ] No indirect costs requested.

S.N. 07/92[redacted]99 EXHIBIT D

Guild Associates, Inc.
4089 North Leap Road
Hilliard, OH 43026
Phone: (614) 876-5252
FAX: (614) 876-5828

March 24, 1992

Mr. Frank H. Foster, Esq.
Kremblas, Foster & Millard
Attorneys-at-Law
7632 Slate Ridge Boulevard
Columbus, Ohio 43068

Dear Frank,

Novel Bone Replacement Technology

Attached, you will find recent correspondence I have initiated with the Army's Medical R&D Command. The document describes an amalgamation of technologies which together appear to have great potential for bone replacement and hard tissue reconstruction. The problem, as I see it, is that the pieces individually are well established.

Frank, you know the approach I typically try to employ, i.e., file a disclosure with minimal information and then build upon it. Once again, that makes sense in this instance except I believe we will have a crude demonstration of at least a portion of the concept available in the next 60 days or so.

Because the project we will propose will involve a wide-ranging group of people who can exploit the idea if we don't protect it, I feel we should get something on file relatively quickly. However, at least in this instance, we should have reasonable reduction-to-practice data available within a reasonable time period.

Can you get a bear–bones filing going for us?

With best regards,

Salvatore T. (Ted) DiNovo
President and Chief Executive Officer

STD/BKH

Enclosure: STD Cover Letter and Preproposal, MRDC, 3/23/92

Guild
Associates, Inc.
4089 North Leap Road
Hilliard, OH 43026
Phone: (614) 876-5252
FAX: (614) 876-5828

March 23, 1992
(COPY)

4/21/92
Laurel
- Was reviewed – to be of interest.
- Send to Letterman for reviews. (Last week – Coordinate –)
Mick May

5/28/92
- Letter – 22 May
- Of interest
- Reviews pulled Sept/Oct '92
Full proposal?

Commander
U.S. Army Medical Research and Development Command
Broad Agency Announcement Program
ATTN: SGRD–ACQ–BA
Fort Detrick
Fredrick, Maryland 21702–5012

Gentlemen,

Novel Bone Replacement Technology

Guild Associates in collaboration with several eminent independent scientists and engineers is pleased to offer a preproposal ***"Rapid Prototype Techniques Applied for Customized Hard Tissue Reconstruction"***. This technology offers military medicine a novel opportunity to lead the forward advance of hard tissue replacement.

Because of the significance of this development, Guild has sought out and established collaborative arrangements with leaders in the disparate technologies which must be organized and integrated to make this development successful. Guild is widely recognized for its integration talents and has, for example, completed the successful development of the Field Medical Oxygen Generation (FMOGDS) system for the MRDC. As originator of this innovation , Guild will be the prime contractor in a proposal we will submit.

We are most anxious to proceed with a proposal covering this technology. As a matter of fact, I will be in Maryland in early April and would be most pleased to meet with the technical staff to elaborate on this document if the opportunity is available. Frankly, if there is strong interest on the Army's behalf, such a meeting can include several key members of the team if appropriate.

We look forward to an early favorable response on this important development opportunity.

With best regards,

Salvatore T. (Ted) DiNovo
President and Chief Executive Officer

STD/BKH
copies:

RAPID PROTOTYPE TECHNIQUES APPLIED FOR CUSTOMIZED HARD TISSUE RECONSTRUCTION

Wounds of war have always horrified civilian populations. Indeed, for all human history, the recognition of attendant physical mutilation has probably been the single most effective limitation on the frequency and scale of conflicts. It is only within the past century that even crude forms of reconstructive surgery were practical. However, the parallel revolutions in computer science and human–focused biotechnology now open an unprecedented opportunity to modern military medicine: to make a wounded soldier whole and functional to a degree that rivals mythology. This project, pursued with an amalgamation of eminent researchers in several critical fields, has as its objective establishing the fundamental science and engineering necessary to demonstrate the radical departure and promise offered in these rapidly developing fields.

Guild Associates, working with several collaborators, has conceived a strategy for a novel therapeutic approach that will create customized prosthetic devices for hard tissue reconstruction. Guild's team believes that *rapid manufacturing technology* can produce implants that *reproduce original tissue size and shape* while simultaneously *maximizing the rate and quality of cell-mediated hard tissue healing*. The Guild concept requires integration of several independently developing technologies designed to:

1. provide physical characteristics of the patient's original hard tissue,
2. permit customized manufacturing by modern techniques and,
3. optimize the rate of healing by incorporating the patient's own bone–producing cells into the implant.

The following sections briefly sketch primary technical issues which will be addressed in a comprehensive proposal.

Imaging Technology

1. Define hard tissue characteristics (size, shape, porosity, etc.) before the trauma occurs ("pre-trauma" file) by archival use of available imaging techniques (CT, MRI, etc.)
2. Define loss of hard tissue by imaging in the locale of the affected tissue after the injury ("post-trauma" file)
3. Specify the physical properties of the customized prosthetic device by comparison of the pre–trauma and post-trauma files to produce a solid model "design" file. This specification may also involve secondary manipulation of the files to assist in surgical implantation and to compensate for anticipated healing process.

Rapid Manufacturing Technology

4. Mathematically process the design file to produce a "sliced file" that is then used to direct a "rapid manufacturing" system to construct a precise replica of the design file in a resorbable ceramic material to produce the implant.
5. Implement a proprietary process which reproduces the unique porosity characteristics (potentially adaptable to specific patients) of the missing hard tissue structures.

Autologous Cell Therapy

6. Culture autologous cells, derived from the patient's post–trauma tissue, then "seed" the cells onto the ceramic matrix under conditions appropriate to maximize cell attachment and function. The implanted cells will rapidly begin producing new bone while other natural process slowly degrade and remove the specialized ceramic matrix.

7. Implant the cell-seeded prosthesis at the trauma site and begin appropriate rehabilitation therapy.

PROJECT STRUCTURE

Guild Associates

The concept described in these paragraphs was originated by engineers at Guild Associates and has been extended and refined by other team members. Guild Associates is well–known to the professional staff at Fort Detrick. The company was successful early in the SBIR program, completing a project to develop a small oxygen generator for use at forward treatment facilities such as battalion aide stations. In 1985, Guild along with two major defense contractors (Litton's Clifton Precision and Pall Corporation) was awarded a contract to develop the FMOGDS oxygen generation system. In a fly–off competition, Guild's system was chosen over that of the other two contractors based upon a comprehensive comparison matrix that contained 52 elements. Undoubtedly, a primary factor in the decision was the success enjoyed by Guild's unit in round–the–clock field trials, a fate not shared by systems produced by the other two candidates. As a result of its performance, Guild was awarded a Phase II contract which was recently completed. The best testimony to the company's success is that the system was recently type classified at an IPR, with all three voting members concurring. In total, Guild's FMOGDS project was funded at nearly $10 million.

Guild's success has not been limited to Fort Detrick. Within the past several years, Guild has been awarded multi–million dollar contracts by both Natick and Edgewood. In these projects, Guild has retained the fervor and commitment to project goals that characterized its work on FMOGDS. We will supply the names of past and current project officers for independent assessment of our performance with our proposal.

Major Project Collaborators

Guild has understood since its inception the importance of building a top–notch, multi-disciplinary team to undertake complex projects such as discussed here. For example, in Guild's FMOGDS contract, Guild employed Battelle and Rockwell International to undertake key tasks such as human engineering, logistics and similar specialities.

While the demands of the proposed project are clearly different in the context of professional disciplines, the commitment to bring into the effort those who know a required discipline is no less important. Thus, Guild has assembled a team of medical and imaging professionals composed of leaders in their respective fields.

Technological Specialists

The following technologists have been involved in some aspects of the project development effort to date. Depending on the scope of the project and the project schedule, each may become involved to a greater or lesser extent.

Dr. David Fink, Bio–Integration, Inc.

After nearly 20 years culminating as a senior researcher and research manager at Battelle, Dr. Fink founded Bio–Integration, Inc in 1986 as a mechanism for offering consulting services in the general field of medical devices involving biological interactions with other physical and chemical systems. Dr. Fink is also an Adjunct Assistant Professor in the Department of Biology at Case Western Reserve UNiversity and has developed a close working relationship with the Skeletal Research Center at CWRU. A detailed resume is attached.

Thomas J. Ward, P. E., Ward Engineering

An acknowledged leader in advanced manufacturing technology, Mr. Ward recently led Battelle's efforts in the rapid prototyping manufacturing (RPM) area. As his resume indicates, his experience includes numerous projects in both industrial RPM techniques (primarily related to generating data files supporting RPM applications) and in medical device development. Again, his resume provides major details.

Orthopaedic Research

Dr. Steven Goldstein, Ph.D. Director
Biomechanics, Trauma and Sports Medicine Laboratory
University of Michigan Medical School
Ann Arbor, MI

Dr. Goldstein is Director of the Biomechanics, Trauma, and Sports Medicine Laboratory at the University of Michigan Medical School, one of the leading centers dedicated to the analysis of structure, biomechanics and pathology of the skeletal system. The Laboratory has extensive equipment and resources including materials testing facilities, computer network, microcomputer (e.g., very fine grain resolution) tomography scanner and microdcopy facilities, all of which are available to the proposed program.

Cell Culture and Developmental Biology

Dr. Arnold I. Caplan, Ph.D.
Skeletal Research Center
Department of Biology
Case Western Reserve University
Cleveland, Ohio

Dr. Caplan, Director of the Skeletal Research Center at Case Western Reserve University, leads a premier research team examining the cell biology of skeletal tissue and originating cell therapy approaches for skeletal defect repair. Investigations of cell seeding on ceramic implant devices would be conducted at this center during the proposed program.

Imagery-to-Manufacturing Conversion

Mr. Michael Marshall
Laser Design Inc.
Minneapolis, Minnosota.

Mr. Marshall has worked in the field of computer imaging technology for over 12 years. He is the first major author of the three dimensional manipulation package, ***Data Sculpt.*** This package will be used to translate imaging data to sliced data for rapid manufacturing.

PROJECT STRATEGY

The proposed strategy for treatment of traumatic or surgical injuries involving hard tissue loss is based on the hypothesis that therapy will optimally treated by a prosthesis:

1. matched to the precise anatomical dimensions of the original tissue (*or* that may be modified to compensate for anticipated healing responses or to provide for surgical assist-structures)

2. composed of bioresorbable ceramic materials that exhibit:

   i. biomechanical properties similar to bone,

   ii. physical and surface properties that facilitate bone cell function, and

   iii. slow resorption to allow replacement by native bone structures.

3. designed to be seeded with autologus cells in order to maximize the rate of colonization of the ceramic matrix and to direct the production of new bone.

EXHIBIT E
Ser. # 07/829,449

Fax Cover Sheet

From

Tom Ward
Ward Engineering Inc.
P.O. Box 12533
1363 West First Avenue
Columbus, Ohio 43212
614-486-8008
Fax: 486-1116

To

Ted Dinovo
876-5252
Fax:876-5828

5 Pages Transmitted

(Including this cover page)

Date

04/02/92

Ted:
Here is my initial write up, please review and comment ASAP.
Thanks. Tom

Transformation of Bone CT Image to a Polymer Free Form Bone Reproduction

Technical Plan Discussion

The transformation of a CT bone image to a polymer free form reproduction is a feasible task. Our proposed scenario for the process is outlined in figure X. The following is a step by step discussion of the proposed process. The discussion includes anticipated problems and concerns and specific solutions and recommendations to each.

We believe that the key aspects of this research are the segmentation process, this is where the bone is regonized and and seperated from the other tissues in the image, and the reproduction of a smooth bone surface, which entails the manipulation of the data after segmeatnation. We plan to run through the process at least three times. Each successive process run being more difficult than the last in both the recognition of bone and the reproduction of the bone.

During the first iteration process we will use approximately 1 inch of the mid section of a canine femur. This simple bone section is used because it has minimal surface features and the perimeter of the bone is well defined and easily recognizable during the transformation process. It is expected that a minimum number of scans (10 - 20) can be used.

During the second iteration we will use the distal end of a canine femur. This bone will also still have tenons attached to it. The purpose of this test is to recognize the bone from the tendons, and to form a smooth, accurate bone end from the CT data. The presence of the articular and fossa surfaces, along with the attached tendons will increase the complexity of this iteration over the first. This will be the first test of the segmentation process.

During the third iteration we will scan a non dissected canine limb. The propose of this test is to segment the bone completely form the surrounding tissue and adjoining bones. The presence of adjoining bones, cartilage, and attached tendon and muscle will increase the complexity of this recognition process over the second. The data files will also grow dramatically due to the increased volume of the CT scan data.

Process Discussion

During the first two iterations, the bone will be prepared by drilling and reaming two .125 inch holes which are mutually orthogonal. These holes will serve as reference datums for quantitative measurement.

The bone will scanned at a CT scan line distance of 1 to 2 mm. The normal of the scan sections will be parallel to the bone axis. The output of the CT scanner will be 512 by 512 arrays 16 bit grey scale data. The CT data will be translated to a TIF format using previously developed code. The TIF formatted file will be imported to Datascuplt. DataSculpt is a three dimensional data manipulation package that will be used to process the CT data. This software runs on a Silicone Graphics Personal Iris computer.

Internal to the data manipulation package each scan will be manipulated so that the perimeters of the solid areas of the bone are defined. This process will be performed using both Datasculpt and application specific code. DataSculpt is able to recognize the grey scale information and draw perimeter splines about the information. After the perimeterization is complete the perimeters will be manipulated to decrease the amount of data to be processed, while maintaining the integrity of the data. At this point the amount of data will be at least two magnitudes smaller than received from the CT scan.

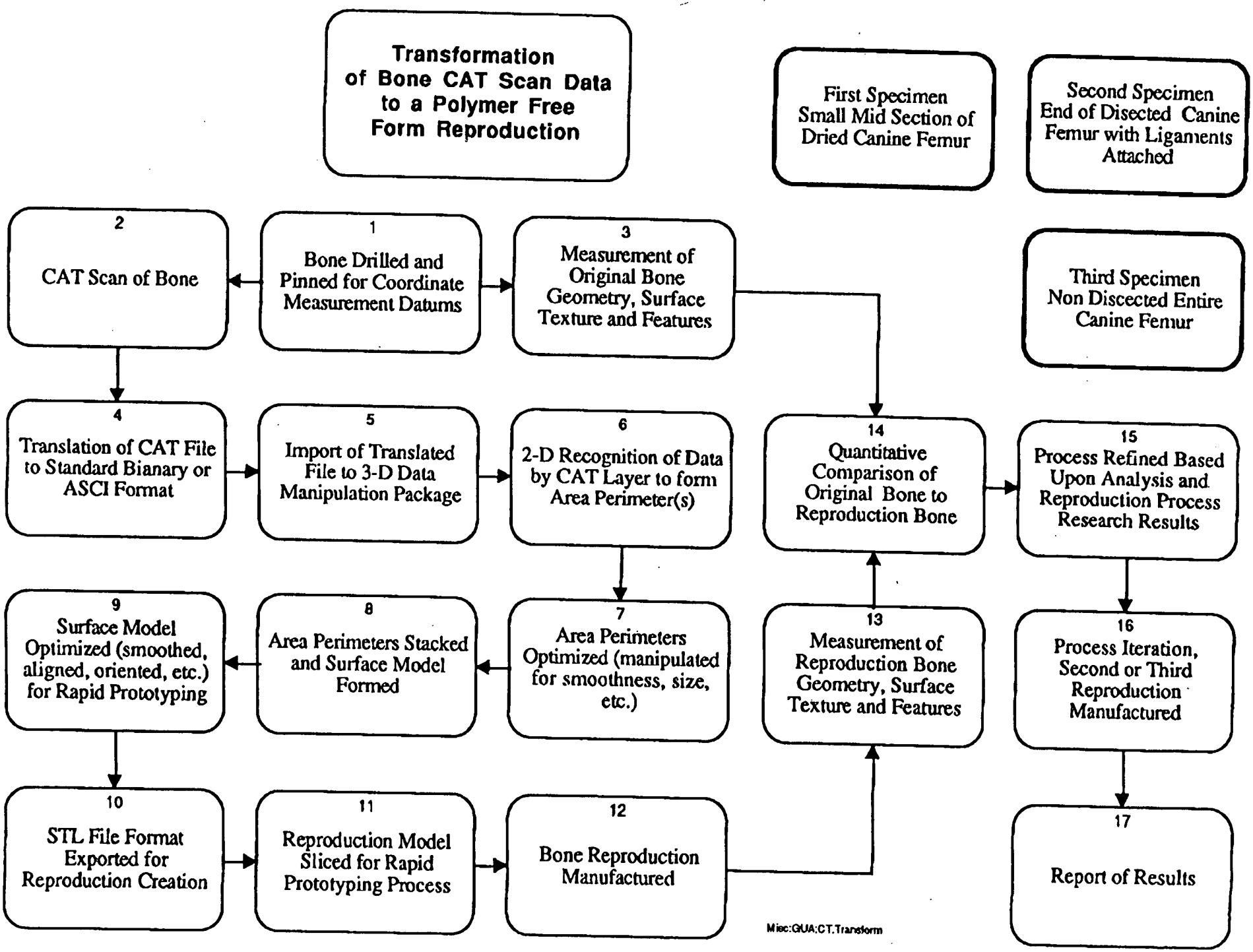
The area perimeters will be rejoined to form a wire frame of the bone. At this point the data spline points will be aligned to prevent aliasing of the surface of the model, and the resolution of the model will be determined. During our first run we expect to working in the 20 to 50 mil. resolution. In subsequent runs we expect to be able to converge on the rapid prototyping resolution of 5 mils. Computer processing speed and disk space can become critical during this process. If a satisfactory final resolution can not be reasonably made due to exorbitant processing times, then an additional small part will be manufactured to the high resolution, while the other models are reproduced to a lower resolution.

A surface model will be made from the wire frame data. The surface model will be composed of triangles. The surface model will then be translated to STL format for rapid prototyping. This data will be sent to the DTM corporation in Austin Texas for prototyping. DTM is a manufacturer of rapid prototyping apparatus. Although they are not as well known as 3-D Systems, thier process shows promise for materials other than photosensitive polymers. Another advantage of

the DTM process is that model supports are not needed. It is expected that four of each model will be reproduced.

During the first two iterations the scanned bone will be quantitatively measured using the holes drilled as datums. Surface texture will be measured for the different areas on the bone surface. When the produced model is returned from DTM the model will be measured and compared to the original bone.

Depending on the results of each iteration, the subsequent iteration procedures will be modified. All major problems will be resolved during a given iteration before the following iteration takes is undertaken.



Ser. # 07/929,449 EXHIBIT F

OUTLINE OF PHASE-1 SBIR PROPOSAL TO HHS DJF 4/7/92

TENTATIVE TITLE: FREE FORM MANUFACTURING OF CUSTOM CERAMIC IMPLANTS

FACE PAGE (Form Page 1) **Guild**

BUDGET FOR PHASE 1 (Form Pages 3 and 4) **Guild**

OTHER GRANT AND CONTRACT SUPPORT (Form Page 3) **Guild and TW?**

BIOGRAPHICAL SKETCHES AND BIBLIOGRAPHY **Guild**

RESEARCH PLAN

Specific Aims **DF/TW**

* Demonstrate feasibility of converting CT images to FFM protocols
* Compare performance of alternative FFM vendors and technologies
* Select best vendor for Phase 2 project

Significance **DF/TW**

Background; evaluation of current knowledge; commercial opportunities; importance of Phase 1 research to Phase 2 objectives

* Introduction to ceramic implants **DF**
* Introduction to FFM **DF/TW**
* Introduction to CT imaging **TW**

* Potential to produce customized implant devices directly from CT records
* Potential to ceramic implants with greater complexity, controlled porosity, control particle migration, improve strength, better biocompatibility?
* Potential to introduce design changes to CT file

* Phase 1 intended to test feasibility of first step in development
* Add'l R&D (Phase 2 and beyond) needed to determine biocompatibility of materials, manufacturing methods, performance of implants, etc.

RESEARCH PLAN -- continued

Relevant Experience **Guild**

Describe the PI's research experience relevant to the project
(PI = TD or TW??)
Describe FFM experience of TW
Describe input of Fink, FFM vendors (list), and software vendors

Experimental Design and Methods **TW/DF**

Identify specific tasks, procedures and protocols; analysis of data; new methodology & advantages; difficulties and limitations of proposed procedures & alternative approaches

Task 1. CT ---> FFM part (2 or 3 vendors)

1st Iteration -- Mid section of femur (bone only)
2nd Iteration -- Femur + Ligaments/Tendons (simple seg. problem)
3rd Iteration -- Entire thigh (complex seg. problem)

Task 2. Selection of Phase 2 vendor/collaborator & approach

Human Subjects -- none in Phase 1
Vertebrae Animals -- none in Phase 1

Consultants -- Letters of participation & Biosketches
Fink/Bio-Integration **DF**
Ward/Ward Engineering?? if not employee of Guild

Contractural Arrangements **Guild**

Literature Cited **DF/TW**

CHECKLIST **Guild**

EXHIBIT G

Serv. # 07/1929 YGG

Ward Engineering Inc.
P.O. Box 12533
1363 West First Avenue
Columbus, Ohio 43212
614-486-8008
Fax: 486-1116

April 7, 1992

Ted Dinovo
President
Guild Associates Inc.
4089 Leap Road.
Hilliard, OH 43026

Dear Ted:

In response to your request for a hands on demonstration of the CT transformation process I am pleased to submit the attached proposal.

I expect that the work will start on April 8, 1992. It is estimated that the work will be completed by April 30, 1992, at an estimated ceiling cost of $5,000. This estimate will not be exceeded without prior consent of Guild Associates.

It has been a pleasure working with you and I look forward to working with you on this exciting project. If you have any questions please contact me at 614-486-8008.

To initiate this work please sign and return one copy of this letter indicating acceptance of the proposed effort.

Sincerely,

Thomas J. Ward, P.E.

Accepted by:

for Guild Associates

4/8/92

Ward Engineering

Proposal

for

Transformation of a Bone CT Image to a Free Form Polymer Bone Model

to

Guild Associates

4089 Leap Road
Hilliard Ohio

April 7, 1992

Transformation of a Bone CT Image to a Free Form Polymer Bone Model

Introduction

Guild Associates is interested in demonstrating the principles involved in the transformation of a CT image of a bone to a polymer bone model using rapid prototyping techniques. Guild Associates, Collatek, and Ward Engineering are currently involved in a joint venture that may allow them to enter into research in this field. Guild is funding this joint effort. Guild would like Ward Engineering to undertake an initial research effort of transforming a CT file to a polymer bone model using rapid prototyping techniques.

Objective

The objective of this task is to experimentally prove that the transformation of a CT file to a polymer bone model using rapid prototyping techniques is a feasible task using the approach outlined below.

Scope

The scope of this work is limited to the experimental task of transforming a CT file to a polymer bone model using rapid prototyping techniques.

Statement of Work

Ward Engineering will undertake the experimental task of transforming a CT file to a polymer bone model using rapid prototyping techniques. Specifics of the experimental approach are as follows:

- Obtain a CT file of a bone from the Medical College of Ohio
- Work with Laser Design to process the bone data
- Work with DTM to have a sintered polymer bone model produced.
- Report the results of the work to Guild and Collatek.

Deliverables

The deliverables of this work will include the completed model and data files, and a succinct report discussing the research effort. Research data will be delivered to Guild Associates on both 3.5 inch, HD, floppy disks and paper form. The data will be in ASCI or interpretable binary format.

Personnel

This work will be completed under the direction of Tom Ward. Guild Associates staff and Ward Engineering associates will be used as needed to complete the task in a timely and cost effective manner.

Schedule and Costs

It is estimated that the task will span 3 weeks and be completed by April 30, 1992, with an April 8 project start date. It is estimated that the cost of the task will be $5,000.

EXHIBIT H

Ser. # 071929,419

Ward Engineering Inc.
P.O. Box 12533
1655 West First Avenue
Columbus, Ohio 43212
614-486-8008
Fax: 486-1116

September 18, 1992

Ted Dinovo
President
Guild Associates Inc.
4089 Leap Road.
Hilliard, OH 43026

SUBJECT: Results of Transformation of a Bone CT Image to a Free Form Polymer Bone Model

Dear Ted:
I have completed the task "Transformation of a Bone CT Image to a Free Form Polymer Bone Model". Two copies of the discussion of the results of this task are attached to this letter. I have arechived the data files from this project and they are available to you and your associates upon request.

Thank you for funding this effort. It was a pleasure to complete it. If you have any questions, please contact me at 614-486-8008.

Sincerely,

Thomas J. Ward, P.E.

Discussion of the Transformation of a Bone CT Image to a Free Form Polymer Bone Model

The following is a description and discussion of the research which was completed by Ward Engineering. Photographs of the final results of the research are attached. As can be seen in the photos the manufactured part does not include cancellous bone. Construction of this honeycomb type structure will not be possible without much higher resolution scanning data. Furthermore, construction of this type of structure will be very difficult using vectorized information (surfaces, splines, etc.). This structure may be made using straight raster information. I am not aware of an algorithm available to accomplish this task, although I don't believe it would very difficult to complete.

Preparation of Bone

The bone was obtained from a veterinarian surgeon at OSU. The bone was received with excessive flesh attached. The flesh was removed from the bone by boiling the bone in a very strong Tide® Detergent/water solution for 2 hours. This was an excessive amount of time. The bone was probably ready after one half hour. The bone was packed in desiccant and shipped to the Medical College of Ohio for scanning.

Scanning of Bone

The bone was scanned at a resolution of 1mm. on a 3-dimensional grid. The number of data points per scan was 261,000. The resolution of the grey scale was 1/65,500. The area of each scan was 419 sq. in. There are 140 scans in the model. The size of the initial data file from MCO was 72 megabytes. This file was decreased to 14 megabytes by decreasing each scan area to 67 sq. in. This file was small enough to be able to transfer it across the internet to Battelle. This file was further reduced using PKzip 1.0 and transferred to DOS disks. These disks were shipped to Laser Design for data manipulation.

Data Recognition

The data file was read into a SGI Personal Iris Elan computer. Code was written to identify the frequency of the magnitude of each data point. The results of this process were visually inspected, and the two areas of interest were identified. The first area turned out to be the space around the bone. The second area was the bone.

The sequence of numbers which were of interest were between 0 and 2,540. A computer display of all points with magnitudes within this range clearly identified the bone. A single section of the bones was removed and further segmented into twelve additional magnitudes. The results of this

sub-sectioning process indicated that the density of the wall of the bone progressively increased in the radial direction until the center line of the bone wall was reached. The density then progressively decreased until the outside of the bone was reached. Based upon this secondary study we felt that we had good data with the first segmentation process. We were also under severe time constraints and the processing time required to segment the one slice was about 10 minutes. To segment 140 slices would not be cost effective.

Data Perimeterization

The data of interest was to be perimeterized so that a STL file could be successfully made. Various techniques were tried and failed. Most of the problems occurred due mathematical routines in the software. These problems were due to the software being used for a process it was not designed for. Simple changes to the software would allow it to handle the problems which occurred. After much time it was found that a successful algorithm for identifying the outside and inside of the bone was working well enough to complete a 1.25 inch mid-section of the bone.

The data around the ends of the bone was not as consistent as the data in the midsection of the bone. This is due to the unusual curvature, density changes and vascular passages ways. Automation of Perimeterization and data recognition around unusual geometry will be difficult.

The midsection of the bone just below the indexing holes was used as the final modeling area. Each slice was manually perimeterized. Approximately 20 slices were prepared. Near one side of the sample the data was perimeterized for each slice. Near the other side it only every third slice was operated upon. The results of this processing were 40 poly-lines that described the inside and outside of the bone surface.

These two processing techniques were tried to see if there was any qualitative change in the surface of the part if lower resolutions are used. A visual inspection of the part does not indicate any apparent surface difference. This indicates that for relatively smooth bones without much curvature change the amount of collected data can be minimized.

Data Manipulation and STL File Construction

The poly-lines were operated upon so that the each line segment had an equal number of equally spaced points. These curves were then smoothed so that no point would move more than .003 inches. The curves were then redefined in the orthogonal direction, and resmoothed to 0.003 inches. These curves were then used to redefine circular curves spaced equal distantly in the axial direction to 0.01 inches. The bone segment was 1.25 inches long, so 250 new curves were defined.

An STL file was generated from this data. The generation of the STL file was relatively easy compared to the other tasks. However, if we have more complex surfaces such as those that are present on the ends of the bones, the task will become much more complex.

Stereo Lithography Model

The STL file produced by Laser Design was delivered to Alpha Mold in Dayton via 2400 baud modem. Alpha Mold is a rapid prototyping service bureau that has been in the business since 1988. I have never worked with them before and wanted to try their service. They turned the part around in 3 days. Their only comment was that the STL file resolution was much finer than they were used to dealing with. This comment was expected, since very fine resolution is required when no true surface is defined on the part.